Second Primary Cancers Related to Smoking and Treatment of Small-Cell Lung Cancer

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Background: **An increased risk of second primary cancers has been reported in patients who survive small-cell carcinoma of the lung. The treatment's contribution to the development of second cancers is difficult to assess, in part because the number of long-term survivors seen at any one institution is small. We designed a multi-institution study to investigate the risk among survivors of developing second primary cancers other than small-cell lung carcinoma.** ***Methods:*** **Demographic, smoking, and treatment information were obtained from the medical records of 611 patients who had been cancer free for more than 2 years after therapy for histologically proven small-cell lung cancer, and person-years of follow-up were cumulated. Population-based rates of cancer incidence and mortality were used to estimate the expected number of cancers or deaths. The actuarial risk of second cancers was estimated by the Kaplan–Meier method.** ***Results:*** **Relative to the general population, the risk of all second cancers among these patients (mostly non-small-cell cancers of the lung) was increased 3.5-fold. Second lung cancer risk was increased 13-fold among those who received chest irradiation in comparison to a sevenfold increase among nonirradiated patients. It was higher in those who continued smoking, with evidence of an interaction between chest irradiation and continued smoking (relative risk = 21). Patients treated with various forms of combination chemotherapy had comparable increases in risk (9.4- to 13-fold, overall), except for a 19-fold risk increase among those treated with alkylating agents who continued smoking.** ***Implications:*** **Because of their substantially increased risk, survivors should stop smoking and may consider entering trials of secondary chemoprevention. [J Natl Cancer Inst 1997;89: 1782–8]**

An increased risk of second cancers has been reported in patients who have been treated for small-cell lung cancer *(1–9)*, even though survival is only 15%–25% at 2 years among patients with limited-stage disease, and 0%–3% among those with extensive disease *(10,11)*. Most commonly reported cancers with increased risk include smoking-related upper aerodigestive cancers and leukemia *(1–9)*. Researchers' ability to evaluate the contribution of therapeutic regimens to the development of second cancers has been limited by the number of longer term survivors in any one institution and the lack of comprehensive

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See ''Notes'' following ''References.''

treatment information available in population-based registries. To address these limitations, we designed a multi-institutional study of this second cancer risk and the role of treatment in the development of these tumors.

Methods

Patients

Investigators from North American medical centers that previously reported on treatment outcome for patients with small-cell lung cancer at their institutions were invited to participate in this collaborative study. Ten medical centers of the Lung Cancer Working Cadre contributed 611 patients with small-cell lung cancer who survived cancer free for 2 or more years: British Columbia Cancer Agency (212 patients); Mayo Clinic (116); Johns Hopkins Oncology Center (72); National Cancer Institute/National Naval Medical Center (61); Toronto Hospital and Princess Margaret Hospital (50); The University of Texas, M.D. Anderson Hospital (40); Vanderbilt University Medical Center (21); Memorial Sloan-Kettering Cancer Center (21); and University of Maryland Hospital (18). All study subjects had histologically or cytologically confirmed small-cell lung cancer and had participated in clinical trials conducted at the centers from 1973 to 1990. The percentage of the total population of patients with small-cell lung cancer enrolled in clinical trials varied by institution and ranged from about 30% to more than 90%. The survivors of 2 or more years represent, on average, 10%–20% of the patients enrolled in clinical trials in these medical centers. As seen in Table 1, most of the survivors had limited-stage disease.

Medical records were reviewed for each patient and detailed abstract forms were completed that included demographic information; smoking history at the time of diagnosis of small-cell lung cancer and subsequently in follow-up; status at last follow-up; all treatment information; and the histology, site, and documentation of any second cancers. All patients received chemotherapy, and 79% also received some radiation to their chest. Study subjects were followed at least annually as part of usual clinical care. To evaluate chemotherapy, the various combinations were arranged hierarchically. The nitrosourea category contained all combinations that included any nitrosoureas that were received at any time. Alkylating agents were classified as any combination received at any time that included alkylating agents that did not also include nitrosoureas. All combinations without alkylating agents or nitrosoureas were classed as other chemotherapy. Cisplatin was included in the last category.

Table 1. Clinical characteristics of study subjects

Characteristic	No. of subjects,	%
Sex		
Male	335,	55
Female	276,	45
Race		
White	549,	90
Black	34,	5
Asian	11,	2
Other	4,	1
Unknown	13,	2
Stage		
Limited	482,	79
Extensive	128,	21
Status at last follow-up		
Alive, without disease	193,	32
Alive with disease	24,	4
Dead	392,	64
Unknown	2,	0.3
Eastern Cooperative Oncology Group performance status at diagnosis of small-cell lung cancer*		
0	105,	17
1	309,	51
2	106,	17
3	13,	2
4	2,	0.3
Unknown	76,	13

*The ECOG performance scale ranks the ability of a patient to function in daily life. A grade of 0 represents full activity, while a grade of 4 represents complete disability.

A total of 103 second cancers were identified. Eighty-five percent of the reported second cancers were documented histologically. Six nonmelanoma skin cancers and 10 other cancers that occurred less than 2 years after the initial diagnosis of small-cell carcinoma were not included in the analyses because we were interested in evaluating treatment-related cancers. For each second cancer, its relationship to previous radiation fields was established by review of relevant x-ray films, when available. The definition of second lung cancer diagnosis was as previously described *(2)*. Second primary small-cell carcinomas were excluded.

Statistical Analysis

For estimation of second cancer risk, person-years of observation were compiled according to sex, age, and calendar year period from 2 years after diagnosis of small-cell lung carcinoma to the date of the second cancer, last follow-up, or death using the computer program of Monson *(12)*. For mortality analyses, person-years were similarly compiled until the date of last follow-up or death. All of the individuals received initial chemotherapy and many received initial radiotherapy to the chest. For estimation of the risk associated with radiation among those who received later chest radiotherapy, person-years were cumulated in two time periods: Before the onset of radiation, person-years were cumulated and added to the nonexposed group from 2 years after the diagnosis of small-cell cancer until the beginning of radiation to the affected area. After initiation of radiation therapy in the affected area, person-years were cumulated in the radiation-exposed group. Cancer incidence rates from the Surveillance, Epidemiology, and End Results (SEER)[1] Program of the National Cancer Institute specific for sex, age, and calendar year were multiplied by accumulated person-years to estimate the number of cancer cases expected had this group experienced the same cancer risk as the general population *(13)*. Mortality rates from the United States population specific for sex, age, and calendar year were multiplied by accumulated person-years to estimate the number of deaths expected. Statistical methods for risk estimation were based on the assumption that observed cancers and deaths followed a Poisson distribution. Tests of significance and confidence intervals (CIs) for the estimated relative risk (RR) (observed to expected cases) were calculated using exact Poisson probabilities. To obtain excess risk per 10 000 patients per year in subgroups with significant RRs, the expected number of cases was subtracted from the number observed. The difference was divided by person-years of observation, then multiplied by 10^4. Tests for trend and homogeneity were performed using the computer program EPITOME *(14)*. Cumulative probability of developing second cancers was calculated using the actuarial method of Kaplan and Meier *(15)*. Multivariate analyses were conducted using the LIFEREG procedure in SAS (SAS Institute, Inc., Cary, NC) *(16)*.

Results

The clinical characteristics of study subjects are shown in Table 1. Seventy-nine percent had limited-stage disease. The average follow-up was 5.2 years and the average age at diagnosis of small-cell lung cancer was 61 years. The cumulative person-years of observation, 2 or more years after the diagnosis of small-cell lung cancer, were 1900. Overall, the risk of any second cancer was increased 3.5-fold in this group of patients, translating to 327 excess cancers per 10 000 person-years (Table 2). Smoking-related cancers (lung, head and neck, larynx, bladder, esophagus, stomach, pancreas, and kidney) were disproportionately represented, with a sevenfold increase (95% CI = 5.2–8.7). Cancers not related to smoking were not significantly increased (observed/expected [O/E] = 1.5; 95% CI = 0.98–2.2).

Most of the increased risk was due to 51 second lung cancers. Of these, 51% (n = 26) were squamous cell carcinomas; 25% (n = 13) were adenocarcinomas (including bronchoalveolar); 18%

Table 2. Estimated relative and absolute risks of second cancers following small-cell cancer of the lung

Site or type of second cancers	Observed	Observed/ expected	95% confidence interval	Absolute risk*
All cancers	87†	3.5	2.8–4.3	327
Trachea and lung	51	11	8.4–15	245
Digestive tract	9	1.6	0.7–3.0	
Acute nonlymphocytic leukemia	5	25	8.0–58	25
Larynx	4	11	2.9–27	19
Female breast	4	1.5	0.4–3.8	
Bladder	3	2.2	0.5–6.5	
Connective tissue	2	22	2.5–80	10
Male genital	2	0.5	0.1–1.8	
Male breast	1	33	0.4–186	
Female genital	1	0.8	0.0–4.3	
Kidney	1	1.6	0.0–9.0	
Melanoma	1	2.1	0.0–6.5	
Brain	1	3.5	0.0–27	
Lymphoma	1	1.3	0.0–7.3	

*Excess risk per 10^4 persons per year.
†Includes one metastatic squamous cell carcinoma of unknown primary.

(n = 9) were carcinomas (non-small-cell), not otherwise specified; 4% (n = 2) were large-cell carcinomas; and 2% (n = 1) were carcinoids. Squamous cell cancers occurred more frequently among men (n = 20) than among women (n = 6), whereas adenocarcinomas occurred more frequently among women (n = 9) than among men (n = 4). The cumulative risk of a second lung cancer was 32% ± 5% at 12 years (Fig. 1) and did not appear to reach a plateau. RRs of both second non-small-cell lung and laryngeal cancers were similar (Table 2). Although the RRs of lung cancer appear to differ between men (O/E = 8.1; 95% CI = 5.4–12) and women (O/E = 19; 95% CI = 12–29), this difference was due to the lower population rates among women. Incidence rates per person-years of observation were equivalent in the two study groups made up predominately of smokers. Although the numbers were small, there were quite high risks of both acute nonlymphocytic leukemia (O/E = 25) and connective tissue sarcomas (O/E = 22) that were potentially treatment related.

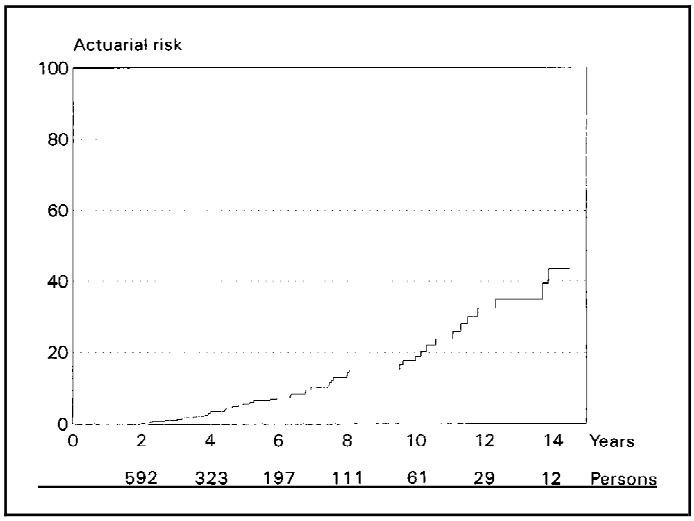

Fig. 1. Actuarial risk of second non-small-cell lung cancer. The first *x* axis shows the time in years; the second the number of persons remaining in the cohort. The *y* axis is the cumulative percent of non-small-cell lung cancer. The actuarial risk at 12 years was 32% ± 5% and at 14 years was 44% ± 8%.

Of second lung cancers, 47% occurred within the radiation treatment port for small-cell cancer; 18% were at the edge of the port; 10% received possible scatter; and 25% received no radiation. There was no significant relationship between the location with respect to radiation port and tumor histology. The risk of second lung cancers increased significantly over time, from a ninefold increase (95% CI = 5.4–13) at 2–4 years after the diagnosis of small-cell lung cancer, to a 12-fold increase (95% CI = 7.4–19) at 5–9 years, to a 25-fold increase (95% CI = 12–46) at more than over 10 years (chi trend; $P<.005$).

When we evaluated risk by radiation status, patients irradiated in the chest (n = 471) were at a 13-fold increased risk of developing a second lung cancer (O = 43; 95% CI = 9.4–17) compared with a sixfold increased risk (O = 8; 95% CI = 2.9–13) among those who were not irradiated (n = 127). The rate ratio of those receiving chest irradiation compared with those not receiving radiation was 1.8 (95% CI = 0.9–3.9). This difference was not due to differences in survival between the irradiated and nonirradiated groups. Among those patients receiving chest irradiation, 6% of the total person-years accrued after 10 years; among those without chest irradiation, 8% of the person-years accrued after 10 years. Risks increased significantly over time among those patients receiving chest radiation therapy from a 10-fold increase (95% CI = 5.8–15) at 2–4 years after the diagnosis of small-cell lung cancer, to a 15-fold increase (95% CI = 8.5–24) at 5–9 years, to a 30-fold increase (95% CI = 13– 58) at more than 10 years (chi trend; $P = .006$). Risks increased somewhat over time even in those patients not receiving chest irradiation (2–4 years, O/E = 5, 95% CI = 1.0–15; 5–9 years, O/E = 6.4, 95% CI = 1.3–19; and ⩾10 years, O/E = 15, 95% CI = 1.8–56), but the trend was not significant (chi trend; $P = .29$).

The risks of a second lung cancer varied by smoking status (Table 3), with no second lung cancers occurring in the small number of patients who were nonsmokers. Average pack-years at the time of diagnosis of small-cell lung cancer did not vary significantly by sex or smoking status among those who had smoked cigarettes. In those who stopped smoking prior to diagnosis of small-cell cancer (mean pack-years = 46 ± 28), risks were stable over time. In those who stopped at the time of small-cell diagnosis (mean pack-years = 53 ± 24), risks increased over time (chi trend; $P = .009$). The highest risks were among those continuing to smoke after small-cell diagnosis (mean pack-years = 53 ± 24).

The risks of a second lung cancer did not vary significantly by pack-years at the time of small-cell diagnosis (Table 3), with no evidence of trend in increasing tertiles (chi trend; $P = .44$). On average, those continuing to smoke after diagnosis of small-cell lung cancer accrued an additional 6 ± 8 pack-years (range, 1–26). Risks were virtually unchanged when total pack-years, which included smoking after small-cell cancer, were evaluated similar to pack-years before diagnosis. To obtain more stable estimates of risk related to both smoking status and pack-years of smoking, we combined all who had stopped smoking into one category. Among those who continued smoking, the risks were higher but not significantly different in each tertile of pack-years compared with the risks in those who had stopped smoking.

Table 3. Estimated relative risk of a second lung cancer by smoking status, by tertile of pack-years before small-cell lung cancer (SCLC) diagnosis, and by smoking status and tertiles of pack-years*

	Observed	Observed/expected	95% Confidence interval	Absolute risk†
Smoking status				
Nonsmoker (n = 13)	0			
Stopped >6 mo before SCLC (n = 144)	11	9.4	4.7–17	245
Stopped at time of SCLC (n = 181)	13	9.9	5.3–17	187
Continued (n = 214)	24	17	11–26	351
Unknown (n = 46)	3	7.5	1.5–22	156
Tertiles of pack-years				
First (mean = 29 ± 8, n = 159)	10	12	5.8–22	177
Second (mean = 44 ± 4, n = 203)	18	11	6.5–17	281
Third (mean = 77 ± 25, n = 180)	21	15	9.0–22	333
Stopped smoking				
First tertile (n = 101)	3	5.2	1.0–15	76
Second tertile (n = 97)	9	9.1	4.2–17	259
Third tertile (n = 99)	10	13	6.0–23	283
Continued smoking				
First tertile (n = 41)	6	27	10–59	386
Second tertile (n = 75)	7	14	5.6–29	313
Third tertile (n = 64)	11	21	10–37	473

*Numbers do not sum to 611 because study subjects with missing critical data were not included.
†Excess risk per 10^4 persons per year.

Excluding patients from the National Naval Medical Center [the group in which the continued smoking effect was first described *(1)*] did not change the magnitude or pattern of risks.

To evaluate the combined effects of smoking status and radiation, we used the same smoking status categories, stopped and continued (Table 4). The three patients who developed a second lung cancer—but whose smoking status was unknown—all received chest irradiation. Among those who stopped smoking, the risks were similar in those who did and did not receive radiation therapy. Trends over time were similar and not significant for either group. Among those continuing to smoke, the risks were much higher among those treated with chest radiotherapy and increased significantly over time (chi trend; $P = .02$). We modeled the data to evaluate the interaction of smoking and chest irradiation. Although the interaction was substantial, it did not reach statistical significance because of the relatively small numbers of events.

Overall, the type of chemotherapy (nitrosoureas, alkylating agents, or other) was not associated with a significant difference in risk (Table 5). The numbers prohibited stratification on radiation and smoking simultaneously in addition to chemotherapy. Risk did not vary substantively by radiation status for those treated with nitrosoureas but did increase over time slightly in those also receiving chest irradiation. Smoking status did not alter risks in combination with nitrosoureas. For alkylating agents, risk appeared higher in those also treated with chest radiotherapy, and risks increased from 6.7 (95% CI = 2.1–16) in the first 5 years to 24 (95% CI = 6.3–60) over 10 years (chi trend; $P = .04$). Among those study subjects treated with alkylating agents, risk varied by smoking status. Those who continued to smoke were approximately fourfold more likely to develop a second lung cancer than those who had stopped prior to diagnosis of small-cell lung cancer. We modeled the data to evaluate the interaction between smoking and alkylating-agent chemotherapy. Evidence for an interaction was substantial, but not statistically significant. For those receiving other chemotherapy, only one in the small group who did not receive chest irradiation developed a second lung cancer. Risks were higher in those receiving radiation therapy to the chest, with a nonsignificant increase over time. Continued smoking also increased the risk of lung cancer in this group.

We also assessed the relationship of treatment to other second cancers. All but one of the acute nonlymphocytic leukemias occurred after treatment with nitrosoureas (O/E = 80; 95% CI = 22–205) as did the single myelodysplasia. The other leukemia occurred after treatment with alkylating-agent chemotherapy (O/E = 11; 95% CI = 0.2–63). No leukemias were related to treatment with etoposide and cisplatin alone, but the number of study subjects in this category was small. If the leukemia rate in the ''other chemotherapy'' group were equivalent to that in the

Table 4. Estimated relative risk of second lung cancer by smoking status and chest irradiation*

	Observed	Observed/expected	95% confidence interval	Absolute risk†
Quit smoking				
No chest irradiation (n = 70)	6	9.1	3.3–20	193
Chest irradiation (n = 261)	18	9.4	5.6–15	207
Continued smoking				
No chest irradiation (n = 42)	2	5.9	0.7–21	
Chest irradiation (n = 172)	22	21	13–32	419

*Numbers do not sum to 611 because study subjects with missing critical data were not included.
†Excess risk per 10^4 persons per year.

Table 5. Estimated relative risk of second lung cancer by type of chemotherapy and chest radiation or smoking status

	Observed	Observed/expected	95% Confidence interval	Absolute risk*
Nitrosoureas (n = 130)	15	13	7.5–22	286
No chest radiation (n = 19)	2	9.3	1.0–33	179
Chest radiation (n = 111)	13	14	7.6–24	313
Quit smoking >6 mo before SCLC† (n = 29)	3	11	2.2–31	337
Quit smoking at SCLC diagnosis (n = 40)	5	14	4.4–32	254
Continued smoking (n = 45)	5	14	4.6–34	289
Alkylating agents (n = 249)	20	9.4	5.8–15	205
No chest radiation (n = 68)	3	4.6	0.9–13	
Chest radiation (n = 181)	17	12	6.8–19	255
Quit smoking >6 mo before SCLC (n = 56)	3	5.2	1.0–15	133
Quit smoking at SCLC diagnosis (n = 87)	6	9.3	3.4–20	172
Continued smoking (n = 75)	10	19	9.1–35	389
Other chemotherapy (n = 187)	13	11	6.0–19	242
No chest radiation (n = 20)	1	4.3	0.1–24	
Chest radiation (n = 167)	12	13	6.7–23	274
Quit smoking >6 mo before SCLC (n = 54)	3	7.2	1.5–21	182
Quit smoking at SCLC diagnosis (n = 51)	2	6.7	0.8–24	
Continued smoking (n = 78)	8	18	7.8–35	363

*Excess risk per 10^4 persons per year.
†SCLC = small-cell lung cancer.

nitrosourea group, four cases would have occurred. The risk of bladder cancer increased fivefold in subjects treated with alkylating agents (95% CI = 0.98–14). All three bladder cancers occurred in study subjects who received cyclophosphamide and who had stopped smoking prior to or at diagnosis of small-cell lung cancer. Connective tissue cancers (soft tissue sarcomas) were not related to radiation therapy, although one occurred in an area of possible scatter. Both study subjects, however, had received alkylating agents.

Overall, mortality from causes other than lung cancer was increased threefold (95% CI = 2.8–3.8) (Table 6). In those study subjects not receiving chest irradiation, the mortality rate from cardiovascular disease was not increased, but among those who did, the cardiovascular death rate was doubled (95% CI = 1.3–2.7). Deaths from myocardial infarctions were not increased, however. Overall, deaths from organic brain syndrome were increased 17-fold and did not include metastatic disease. Among those patients who did not receive cranial irradiation, central nervous system deaths were doubled, but this was not statistically significant. All such deaths were from organic brain syndrome (O/E = 6.3; 95% CI = 1.7–16). The risk of death from organic brain syndrome was increased 24-fold among those receiving cranial irradiation (95% CI = 15–37; absolute risk = 148).

Discussion

We reported earlier *(1)* that continued smoking increased the risk of a second lung cancer in patients who had been treated for small-cell lung carcinoma. With longer follow-up and larger numbers, we have confirmed these findings. Risk is lowest in those who stopped smoking prior to developing small-cell lung cancer. In those who continued to smoke, risk was approximately doubled overall. Pack-years of smoking prior to development of small-cell lung cancer did not differ between the smoking status groups, but the risks in each tertile of pack-years were higher among those continuing to smoke. The increase in risk among those continuing to smoke could not be explained by the increment in accumulated pack-years. The similar risk of laryngeal cancer and the sevenfold increase of smoking-related

Table 6. Standardized mortality ratios of causes of death other than lung cancer*

Site or cause	Observed	Observed/expected	95% confidence interval	Absolute risk†
Total	150	3.3	2.8–3.8	503
Circulatory system	40	1.7	1.2–2.3	80
ASCVD	14	0.9	0.5–1.5	
Nervous system	29	6.1	4.1–8.9	118
OBS	26	17	11–25	119
Vascular	3	1.0	0.2–2.8	
Respiratory system	18	4.2	2.5–6.6	67
Pneumonia	12	8.9	4.6–16	52
All other cancers	13	1.3	0.7–2.3	
Leukemia and aleukemia	6	13	4.9–29	27
Other infections	7	12	4.7–24	31
Gastrointestinal	6	3.3	1.2–7.1	20

*ASCVD = atherosclerotic coronary vessel disease; OBS = organic brain syndrome.
†Excess risk per 10^4 persons per year.

cancers are consistent with the hypothesis of a field effect, with the entire aerodigestive epithelium at risk. Similar to our findings in a smaller group, most of the excess risk in smoking-related cancers was in sites in the upper aerodigestive tract that were directly exposed to smoke. The single exception was the excess of bladder cancers. It is noteworthy that all three individuals with bladder cancer had stopped smoking but had received cyclophosphamide, a known bladder carcinogen *(17)*. This total group of patients is likely to be representative of survivors of small-cell lung carcinoma, since in most participating institutions, the majority of the total population of patients with small-cell lung cancer were entered in clinical trials.

Chest radiotherapy approximately doubles the risk of a second lung cancer in this population of heavy smokers. This is the same order of magnitude of risk demonstrated after radiation treatment of breast cancer or Hodgkin's disease *(18–21)*. Among subjects who stopped smoking, there appeared to be no additional risk conferred by chest irradiation. Among those who continued, however, there appeared to be synergism between chest radiation therapy and smoking in the development of second lung cancers, as evidenced in the demonstrated risks and the modeled data. This observation is consistent with the enhanced risk of lung cancer among long-term survivors of Hodgkin's disease who smoked *(18)*. Other types of radiation also increase lung cancer risks. Miners who were exposed to radon daughters and who smoked are also at higher risk of lung cancer than nonsmoking miners *(22)*. Although it is speculative, smoking may act as a ''promoter'' in tissues with radiation-induced genomic instability. In these data, the excess risk of a second lung cancer in long-term survivors who received radiation therapy and continued to smoke was more than one in 10 per year.

These data suggest that chemotherapy, particularly alkylating agents, also contributes to the risk of a second lung cancers. Kaldor et al. *(19)* first reported a twofold increased risk of lung cancer following Hodgkin's disease, associated with mechlorethamine and procarbazine treatment. However, smoking information was not available in those study subjects. In these data, neither smoking nor radiation therapy substantially changed the risks associated with nitrosourea chemotherapy. In contrast, radiation therapy doubled the risk in those receiving alkylating agents. There was evidence of interaction of the alkylating agents with smoking, although the data did not reach significance. Those who had stopped smoking prior to diagnosis of small-cell lung cancer had much lower risks of second lung cancer than those who continued smoking. These are the first data suggesting such synergism. Although there was a suggestion of a similar pattern with the ''other chemotherapy'' group, the trends were not statistically significant. These data add to the growing evidence that chemotherapy may affect the risk of solid second tumors as well as of leukemia *(19,23)*.

Acute nonlymphocytic leukemia was related to treatment with nitrosoureas, and to a much lesser extent, to alkylating-agent chemotherapy. The high percentage of individuals receiving nitrosoureas and alkylating agents is related to two factors: the era of treatment that allowed evaluation of late events such as solid tumors and the inclusion of all treatment in the chemotherapy categorization. These data are consistent with previously published information on acute nonlymphocytic leukemia following small-cell lung carcinoma and the literature on treatment-induced leukemias *(17,24)*. In addition, the lung cancer risk following treatment with nitrosourea-containing combinations was not altered by either radiation therapy or smoking in contrast to the increase in lung cancer risk following alkylating-agent chemotherapy with radiation therapy or smoking. The increased leukemia and lung cancer risks associated with nitrosoureas support the observations that nitrosoureas are more potent carcinogens than are alkylating agents. The clinically noted decrease over time in acute leukemia following small-cell lung cancer probably relates to less frequent use of nitrosoureas *(25)*. The risk of leukemia did not vary by total pack-years or by smoking status, although a role for smoking had been previously suggested *(9)*.

The patterns of increased mortality are not unexpected. We could not evaluate precise diagnoses because details of the cause of death were not sought. The increased risk of cardiovascular disease in those treated with chest radiation therapy is somewhat consistent with the increased risk observed in historic Hodgkin's disease cohorts before the left ventricle was shielded *(26)*. Most of those patients, however, were treated at an earlier age. In those data, age at treatment had a profound influence on risk. The level of increased risk is also consistent with a heavy smoking population, but those not receiving chest radiation did not have increased risk of cardiovascular death. Although there was risk of death associated with organic brain syndrome in those who did not receive radiation therapy, the risk was much higher in those who did. Most of those treated with cranial irradiation received it prophylactically.

Although these results suggest that treatment for small-cell lung cancer may affect risk of a second lung cancer and cause other morbidity, these results must be put in context. Small-cell lung cancer is a rapidly fatal disease without therapy. Both radiation therapy and chemotherapy play important roles in the current treatment of lung cancer, and neither should be abandoned. Notably, the effects of both radiation therapy and chemotherapy on the development of second cancers seem to be substantially enhanced in those continuing to smoke. Although based on relatively small numbers, the risk of a second lung cancer is much lower in those who stop smoking. These findings have direct clinical applications: They underscore that one of the most important factors in reducing the risk of second cancers is to stop patients from smoking. The 32% cumulative risk of a second lung cancer at 12 years also indicates that this group may benefit from secondary chemoprevention trials *(27,28)*. Such trials are proposed for patients with small-cell lung cancer who survive, cancer free, for at least 3 years.

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Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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